FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

November 6, 2014

NDA 205353
panobinostat (Farydak)
Novartis

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the Farydak NDA with the Applicant's proposed indication to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Proposed Indication

Farydak, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.

2 Executive Summary

This NDA is primarily based on the randomized, controlled trial CLBH589D2308 (Trial 2308) of 768 patients with relapsed multiple myeloma.

Trial 2308 is a randomized, placebo-controlled, double-blinded, add-on design trial using bortezomib (B) and dexamethasone (D) as backbone therapy. The primary endpoint was investigator-assessed progression-free survival (PFS); the key secondary endpoint was overall survival (OS). PFS was also assessed by independent review committee (IRC) in a sensitivity analysis due to large amounts of incomplete response assessment data.

Efficacy

- Investigator-assessed median PFS difference was 3.9 months: 12.0 months in the panobinostat + BD arm vs. 8.1 months in the placebo + BD arm, with a hazard ratio of 0.63 (95% CI: 0.52, 0.76), *p*-value <0.0001.

- IRC-assessed median PFS difference was 2.2 months: 9.9 months in the panobinostat + BD arm vs. 7.7 months in the placebo + BD arm.

- Immature interim analysis for OS (69% of needed events) demonstrates a median time to event difference of 3.2 months: 33.6 months in the panobinostat + BD arm vs. 30.4 months in the placebo + BD arm.

Safety

- On-study deaths occurred more frequently in the panobinostat + BD arm compared to the placebo + BD arm, 8% vs. 5.1%. On-study deaths within 30 days due to causes other than disease progression occurred in 7% in the panobinostat + BD arm vs. 3.5% in the placebo + BD arm.

- Nonfatal serious adverse events (SAE) occurred in 60% of patients in the panobinostat + BD arm and 42% in the placebo + BD arm. Non-fatal SAEs with a ≥ 5% incidence in the panobinostat + BD arm were pneumonia, diarrhea, thrombocytopenia, sepsis, and fatigue.

- Grades 3 and 4 AEs that occurred more frequently in the panobinostat + BD arm compared to the placebo + BD arm included thrombocytopenia (56.7% vs. 24.7%), neutropenia (23.8% vs. 8.1%), diarrhea (25.4% vs. 7.8%), vomiting

(7.3% vs. 1.3%), nausea (5.4% vs. 0.5%), fatigue (59.6% vs. 24.6%), hypokalemia (19.2% vs. 6.5%) and hyponatremia (9.6% vs. 3.5%). .

- ECG changes that were reported more frequently in the panobinostat +BD arm compared to placebo +BD arm included new T-wave changes (40% vs. 18%), ST-segment depressions (22% vs. 4%), and QT-prolongation (12% vs. 8%).

3 Issues

Given the following benefit-to-risk profile of Farydak:

- An improvement in median progression-free survival of 3.9 months as assessed by investigators or 2.2 months as assessed by independent review committee

- An increased incidence of deaths not due to progressive disease (7% vs. 3.5%) and the observed adverse events of myelosuppression, hemorrhage, infection, gastrointestinal toxicity, and cardiac toxicity

Does the benefit of treatment with Farydak in combination with bortezomib and dexamethasone outweigh the risks for patients with relapsed multiple myeloma?

4 Background

4.1 Multiple Myeloma

Multiple myeloma (MM) is a plasma cell neoplasm characterized by the proliferation and accumulation of clonal plasma cells that produce a monoclonal immunoglobulin. The clinical features of the disease result from bone marrow infiltration by the malignant clone, high levels of circulating immunoglobulin and/or free light chains, and depressed immunity.

MM accounts for approximately 1% of all cancers and 10% of hematologic malignancies. An estimated 24,000 new cases of MM will occur in the U. S. in 2014 with an estimated 11,000 deaths. The diagnosis is most common in the 6^{th} and 7^{th} decades of life and approximately 75% of patients are over 70 years of age. Blacks account for twice as many new cases of multiple myeloma than Whites: 12.2 vs. 5.6 per 100,000 men and women per year (Howlader, Noone, et al. 2013).

4.2 Multiple Myeloma Treatment

Treatment of MM is typically initiated when symptoms develop. Patients with symptomatic MM often respond to cytotoxic chemotherapy. However, responses are

often transient and MM is not considered curable with available treatments. Table 1 lists all FDA approvals for multiple myeloma.

Table 1 Currently Available Treatment for Multiple Myeloma

Drug Name *Indication*	Trial Type	Approval *Date, Type*	Approval Basis	Survival Benefit?
Cytoxan (cyclophosphamide) *For treatment of MM*		1959 *Regular*	Case series	NE
Alkeran tablet (melphalan) *For palliative treatment of MM*		1964 *Regular*	Case series	NE
BiCNU (carmustine) *For MM in combination with prednisone*		1977 *Regular*	Case series	NE
Alkeran injection (melphalan) *For palliative treatment of MM for whom oral therapy is not appropriate*	Randomized trial of Alkeran intravenous (IV) injection + pred (n=203) vs. oral melphalan + pred (n=107)	1992 *Regular*	Response rate at 22 weeks: Oral 44% vs. IV 38%	NE
Velcade (bortezomib) *For 3rd line MM*	Single arm trial (n=256)	2003 *Accelerated*	ORR 28%	NE
Velcade (bortezomib) *For 2nd line MM*	RCT of Velcade vs. dexamethasone (n=669)	2005 *Regular*	Median TTP: Velcade 6.2 m. vs. dex 3.5 m. ΔTTP 2.7 m.	Yes HR 0.57, p<0.05 (median f/u 8.3 m.)
Revlimid (lenalidomide) *For 2nd line multiple myeloma, in combination with dexamethasone*	Two RCTs of Revlimid + dex vs. dexamethasone alone (n=341, n=351)	2006 *Accelerated*	Trial 1: Median TTP: Rev+dex 8.5 m. vs. dex 4.6 m. Δ TTP 3.9 m. Trial 2: Median TTP Rev+dex NE vs. dex 4.6 m.	No
Thalomid (thalidomide) *For newly diagnosed MM*	Two RCTs: Thalomid + dex vs. dexamethasone alone (n =207) Thalomid + dex vs. placebo (n=470)	2006 *Accelerated*	Trial 1: ORR: Thal+dex 52% vs. dex 36% Trial 2: median TTP: Thal+dex 22.5 m. vs. dex 6.5 m. Δ TTP 16 m.	Difference not statistically significant

Drug Name *Indication*	Trial Type	Approval *Date, Type*	Approval Basis	Survival Benefit?
Doxil (doxorubicin HCL liposome) *For 2nd line MM (no prior Velcade)*	RCT of Doxil + bortezomib vs. bortezomib alone (n=646)	2007 *Regular*	Median TTP Doxil+bort 9.3 m. vs. bort 6.5 m. Δ TTP 2.8 m.	No
Velcade (bortezomib) *For untreated MM*	RCT of Velcade + melphalan + pred (VMP) vs. melphalan + pred (MP) (n=682)	2008 *Regular*	Median PFS VMP 18.3 m. vs. MP 14 m. Δ PFS 4.3 m.	Yes HR 0.61, p=0.0078 (median f/u 16.3 m.)
Kyprolis (carfilzomib) *For 3rd line MM*	Single arm trial (n=266)	2012 *Accelerated*	ORR (sCR, CR, VGPR, PR): 23%. mDOR: 7.8 m.	NE
Pomalyst (pomalidomide) *For 3rd line MM*	RCT of Pomalyst + dex vs. Pomalyst alone (n=221)	2013 *Accelerated*	PFS not evaluable; ORR (PR, CR): 29% vs. 7%. mDOR for Pom+dex: 7.4 m.	NE

bort = bortezomib, dex = dexamethasone, mDOR = median duration of response, m = months, MM = multiple myeloma, NE = not evaluable, ORR = overall response rate, pred = prednisone, RCT = randomized controlled trial, TTP = time to progression, Δ = difference
[Source: FDA]

4.3 Relapsed Multiple Myeloma Treatment

FDA granted a second-line multiple myeloma indication to three drugs: Velcade, Revlimid, and Doxil. Doxil and Velcade were later converted to regular approval based on randomized, controlled trials.

4.4 Primary Endpoints for Prior Approvals

Recent regular approvals for drugs in multiple myeloma have been supported by improvements in time-to-progression (TTP) or progression-free survival (PFS). Both include objective tumor progression in time from randomization; TTP does not include deaths.

For approved products, differences in median PFS or TTP ranged from 2.8 to 9.2 months in add-on design trials. A 9.2 months difference occurred when dexamethasone alone was used as the comparator regimen. In more recent approvals, an add-on design to a standard chemotherapy regimen, i.e., to bortezomib or to melphalan and prednisone, led to smaller incremental improvements in PFS or TTP. Accelerated approvals have been supported by overall response rate (ORR) results from single-arm trials.

4.5 Major Regulatory Milestones in the Development of Farydak

Table 2 Key Regulatory Activities Related to Clinical Development

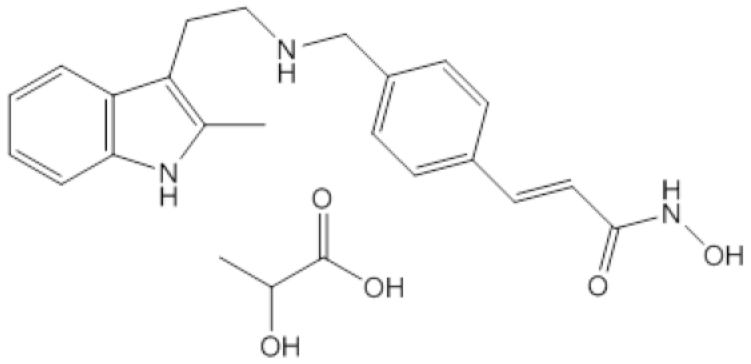
Date	Details
May 2004	Investigational new drug application submitted by Novartis Pharmaceuticals, Corp. for oral LBH589 (panobinostat)
Nov 2006	Special Protocol Assessment non-agreement for proposed single-arm trial in patients with multiple myeloma who have approved and available treatment options. Proposed dose and regimen was not justified nor finalized.
Feb 2012	Meeting to discuss statistical and clinical endpoints in the ongoing Trial 2308.
Feb 2014	Meeting held to discuss content and format of proposed NDA.
Mar 2014	NDA submission. Designated Priority review.
Apr 2014	Expanded access for treatment use protocol allowed to proceed.

[Source: FDA]

5 Drug Description

Panobinostat is a histone deacetylase inhibitor. The chemical name is (2*E*)-*N*-Hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl]prop-2-enamide 2-hydroxypropanoate (1:1). The molecular formula is $C_{21}H_{23}N_3O_2 \cdot C_3H_6O_3$ and the molecular weight is 439.51 g/mol as a lactate [349.43 (free base) + 90.08 (lactic acid)]. The structural formula is shown in Figure 1.

Figure 1 Chemical Structure of Panobinostat



6 Trial

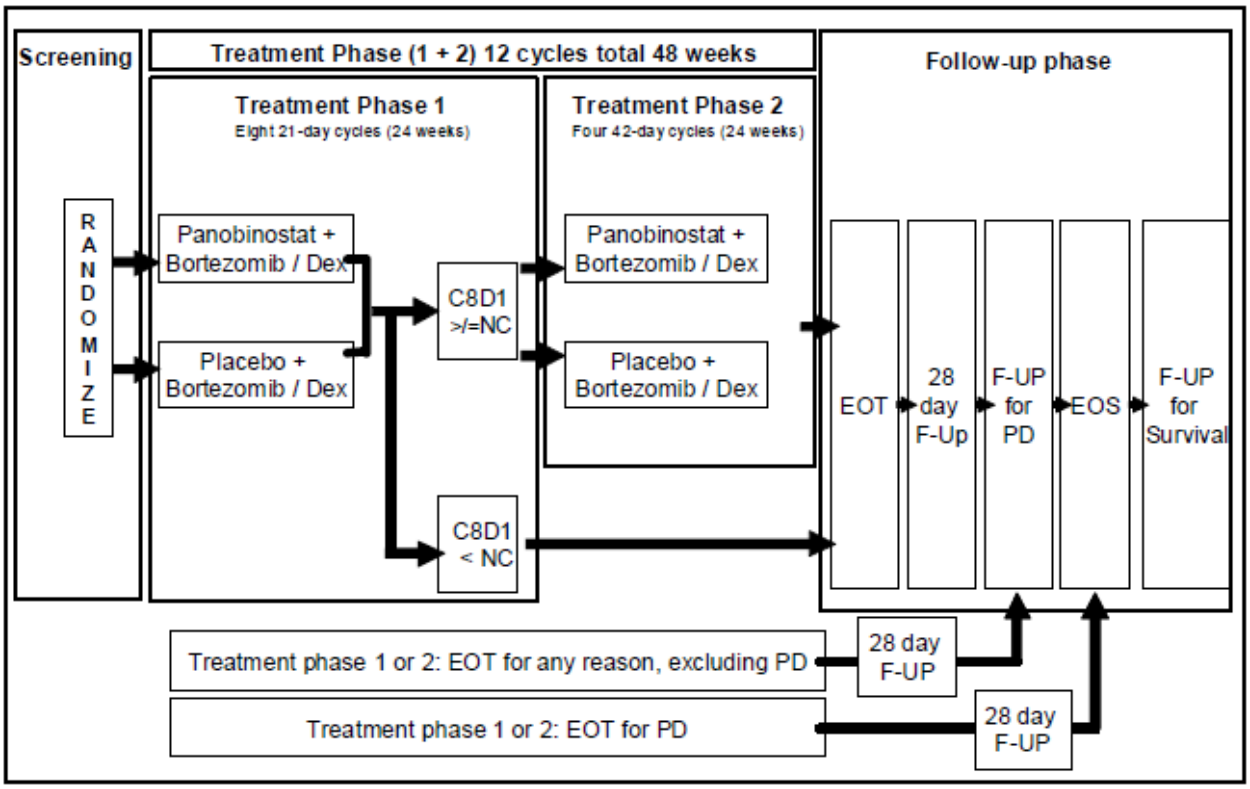
The efficacy of Farydak (panobinostat) was principally evaluated in 768 patients with relapsed multiple myeloma enrolled in a 1:1 randomized, placebo-controlled, double-blinded, add-on design trial using bortezomib (B) and dexamethasone (D) as backbone therapy. The primary endpoint was investigator-assessed progression-free survival

(PFS); the key secondary endpoint was overall survival (OS). Patients with 1 to 3 prior treatments were eligible.

6.1 Trial Design

The PANORAMA-1 trial (Trial 2308) was a multi-center, international trial that was open for enrollment of patients from 2010 to 2012. After screening and consenting, eligible patients were randomized to panobinostat or placebo. All patients were treated with IV bortezomib and oral dexamethasone. Randomization was stratified by the number of prior lines of therapy (1 vs. 2 or 3) and by prior use of bortezomib (yes vs. no).

Figure 2 Study Design Schema



C8D1 = Cycle 8 Day 1 visit; NC = No change (as per mEBMT criteria); EOT = End-of-treatment; F-UP = follow-up; PD = Progressive disease or relapse from CR; EOS = End of Study
[Source: Novartis Clinical Study Report CLBH589D2308, p. 122]

6.2 Study Drug Administration and Schedule

Treatment on protocol was 48 weeks in duration split in two 24-week phases. Treatment phase 1 comprised eight 3-week cycles of panobinostat 20 mg orally 3 times a week for two weeks of 3-week cycles or identical placebo. All patients were given bortezomib 1.3mg/m^2 intravenous (IV) administration twice weekly for 2 of 3 weeks with dexamethasone 20 mg per day for two days with each dose of bortezomib.

After 24 weeks, patients with any treatment response or stable disease, and without Grade 2 or higher toxicity, could continue onto treatment phase 2. In treatment phase 2, bortezomib was reduced to two doses every 3 weeks with dexamethasone; panobinostat or placebo was continued.

Table 3 Treatment Doses and Regimens

Treatment phase 1: Cycles 1-8, 3 week cycles			
Drug	Panobinostat/Placebo 20 mg orally	Bortezomib 1.3 mg/m^2 IV	Dexamethasone 20 mg orally
Regimen, on Days	1, 3, 5, 8, 10, 12	1, 4, 8, 11	1, 2, 4, 5, 8, 9,11, 12

If no change/stable disease or better, and no toxicities ≥ Grade 2, continue on to Treatment phase 2

Treatment phase 2: Cycles 9-12, 6 week cycles			
Drug	Panobinostat/Placebo 20 mg orally	Bortezomib 1.3 mg/m^2 IV	Dexamethasone 20 mg orally
Regimen, on Days	1, 3, 5, 8, 10, 12	1, 8	1, 2, 8, 9
	22, 24, 26, 29, 31, 33	22, 29	22, 23, 29, 30

[Source: FDA analysis]

Dose modifications were allowed for adverse reactions thought to be related to one of the treatment drugs. Dosing adjustments for panobinostat were specified for cytopenias, QTc prolongation, nausea, vomiting, diarrhea, fatigue, and bilirubin, AST, or ALT elevations. Bortezomib was to be modified for cytopenias, febrile neutropenia, peripheral neuropathy, and Herpes zoster reactivation. Dexamethasone modifications were specified for dyspepsia, gastrointestinal (GI) ulcer, gastritis, acute pancreatitis, edema, confusion or mood alteration, muscle weakness, and hyperglycemia.

6.3 Dose Selection

The maximum tolerated dose (MTD) of panobinostat in combination with bortezomib was based on the phase 1b dose-escalation Trial 2207. The trial enrolled 47 patients with relapsed multiple myeloma. Five different dose levels were evaluated (ranges: panobinostat 10-30 mg and bortezomib 1-1.3 mg/m2; three times every week, in six dose-cohorts). The MTD was determined to be 20mg of panobinostat with 1.3 mg/m^2 bortezomib. Responses were seen at all dose levels, with higher response rates observed in dose levels up to panobinostat 20 mg and bortezomib 1.3 mg/m^2.

The MTD regimen was modified for the dose expansion phase: dexamethasone 20mg was added and a 1-week treatment holiday per cycle was introduced. The 1-week rest

period was introduced to manage thrombocytopenia; dexamethasone was added to provide additional anti-myeloma activity. Increased response rates did occur in the dose expansion phase.

Serious AEs occurred more frequently at higher dose levels, as did drug interruptions and discontinuations due to AEs. At the recommended phase 2 dose and schedule, grade 3-4 AEs occurred in 87% of patients, 73% of patients had dose interruptions, and 33% were hospitalized due to adverse events. Given the substantial toxicity observed and number of dose modifications, it is not clear that the correct dose was selected for the phase 3 randomized trial.

Single-agent panobinostat showed only very modest treatment effect in patients with relapsed multiple myeloma. Trial 2203 included 38 patients with relapsed multiple myeloma who received 20mg panobinostat three times a week; only one patient had a partial response, none had a complete response.

6.4 Duration of Treatment

Patients were treated for a maximum of 48 weeks or until the development of progressive disease (PD), unacceptable toxicity, or consent withdrawal.

6.5 Trial Endpoints

The primary endpoint was PFS based on an investigator assessment of modified EBMT[1] criteria (Bladé, Samson, et al. 1998). Overall Survival was the key secondary endpoint. Additional secondary endpoints included overall response rate (proportion of patients with CR, nCR, or PR) and duration of response. Responses were confirmed after six weeks. A protocol amendment established an Independent Review Committee (IRC) assessment of PFS as a sensitivity analysis.

6.6 Major Eligibility Criteria

The population in this trial was comprised of adult patients with relapsed multiple myeloma after 1 to 3 prior lines of therapy, including autologous stem cell transplant.

Required were:

- previous diagnosis of multiple myeloma as per the 2003 International Myeloma Working Group (IMWG) definition
- need for re-treatment per IMWG
- measurable M-protein per IMWG
- ECOG performance status of 0, 1, or 2
- No impaired cardiac function, clinically unstable dysrhythmia, or QT interval prolonging drugs

[1] European Society for Blood and Marrow Transplantation

6.7 Efficacy Evaluation

Clinically relevant endpoints in clinical trials of new drugs for patients with relapsed multiple myeloma, include PFS, TTP, and OS (Anderson, Kyle, et al, 2008). A bortezomib and dexamethasone regimen is considered an effective treatment for patients with relapsed multiple myeloma.

6.7.1 Primary Endpoint: PFS

In Trial 2308, PFS was defined as the time from the date of randomization to the date of the first documented progressive disease or relapse, or death due to any cause. PFS was censored at the date of the last response assessment prior to the data cut-off date or start of new treatment for patients who had not progressed or died.

The analysis plan assumed a median PFS of 10.2 months in the panobinostat + BD arm and 7.5 months in the placebo + BD arm; a difference of 2.7 months with a hazard ratio of 0.74. The planned sample size was 762 subjects to test superiority on 460 events with a stratified log rank test considering a cumulative type 1 error rate of α=0.05, 2-sided. Final enrollment included 768 patients who experienced 467 events at the pre-specified data cut-off date. Efficacy analyses were performed on the intent-to-treat (ITT) trial population of this randomized controlled trial.

6.7.2 Secondary Endpoint: OS

Overall survival was the key secondary endpoint and was only tested after a significant PFS result. The plan for final OS analysis was based on 415 events, testing a difference of 5.4 months with a hazard ratio of 0.73. At the pre-specified data cut-off date for final PFS analysis, the third interim analysis for OS was done. In August 2014, the Applicant amended the protocol to introduce an additional interim analysis for OS when approximately 90% of the target numbers of OS events were reached.

6.7.3 Pre-specified Sensitivity Analysis: PFS by IRC assessment

During an internal audit while the trial was ongoing but after all patients completed treatment, the Applicant identified that not all investigator sites used protocol-defined methods for measuring M-protein: protein electrophoresis (PEP) with quantification of M-protein spike. In 193 patients (25% of the total enrolled) alternative methods were used such as nephelometry or total globulin, or the gamma globulin fraction was used as an indicator for an IgG M-component. Missing assessments occurred in both arms: M-protein measurement was incomplete in 25% of patients on the panobinostat + BD arm and 26% on the placebo + BD arm.

Identification of the protocol deviations prompted the Applicant's Study Steering Committee to recommend an independent review committee (IRC) assess the response data. In this assessment, patients with available M-protein results measured by PEP

were evaluated for response using mEBMT criteria, as done by the investigators. For patients without M-protein measurements, the IRC could assess responses based on principles and intention of the mEBMT criteria. This latitude allowed the IRC to adjudicate disease deterioration by rising M-protein values as progression. In other cases of missing baseline data, the IRC could use post-baseline M-protein values and immunofixation data to determine responses.

6.8 Safety Evaluation

Safety assessments included collection of all adverse events (AEs) and serious AEs. The assessments included regular monitoring of hematology, coagulation, and chemistry panels, and regular physical examinations, including vital signs, body weight, and determination of performance status.

A central laboratory was used for ECG monitoring and review. The screening ECGs were reviewed by the central lab to determine eligibility prior to the first administration of study drug. Subsequent ECGs were obtained day 1 of each cycle, through cycle 8.

AEs were coded using the medical dictionary for regulatory authorities (MedDRA) and were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) scale, version 3.0.

6.9 Patient-reported Outcomes

An exploratory endpoint evaluating health related quality-of-life (QOL) and symptoms of multiple myeloma was included in Trial 2308 using descriptive analysis only:

1. The Quality of Life Questionnaire (QLQ)-C30, released in 1993 by the European Organization for Research and Treatment of Cancer (EORTC) to assess health-related QOL of cancer patients participating in international clinical trials.

2. QLQ-MY20, a patient self-reporting module developed by EORTC to complement the QLQ-C30 for patients with multiple myeloma.

3. Functional Assessment of Cancer Therapy (FACT)/Gynecologic Oncology Group (GOG)-Neurotoxicity (Ntx) Subscale Score, a patient self-reporting questionnaire developed by GOG to assess platinum/paclitaxel-induced neurologic symptoms.

7 Trial Results

The data cut-off date for analysis of Trial 2308 was 10 September 2013. The data cut-off data for the additional OS interim analysis was 18 August 2014.

7.1 Patient Population

The efficacy analysis was based primarily on the intent-to-treat population of 768 patients.

The safety analysis was performed primarily on the 758 patients who received at least 1 dose of panobinostat or placebo in combination with bortezomib and dexamethasone in Trial 2308. Five patients randomized to the placebo arm received at least 1 dose of panobinostat and were included in the panobinostat arm for this analysis.

7.2 Efficacy

7.2.1 Patient Characteristics

Seven percent of patients were from the United States. Enrollment occurred primarily in European (43%) and Asian (29%) countries. The demographic characteristics in the treatment arms were well balanced.

Race and ethnicity differed from the U.S. myeloma population; Black patients are under-represented in this trial. Trial 2308 enrolled 22 Black patients; six were from U.S. sites. The median age of patients in the trial was 63 years, six years younger than the median age at myeloma diagnosis in the U.S. expected from SEER statistics (Howlader, Noone, et al. 2013). Table 4 lists patient demographic characteristics.

Table 4 Demographic Characteristics

	Panobinostat + BD n=387	Placebo + BD n=381
Median age, years (range)	63 (28, 84)	63 (32, 83)
Sex		
Male	202 (52.2%)	205 (53.8%)
Female	185 (47.8%)	176 (46.2%)
Race		
White or Caucasian	249 (64.3%)	250 (65.6%)
Asian	128 (33.1%)	104 (27.3%)
Black or African American	5 (1.3%)	17 (4.5%)
Other	5 (1.3%)	10 (3.8%)
U.S. enrollees	22 (5.7%)	32 (8.4%)

BD = bortezomib + dexamethasone
[Source: FDA analysis]

Prior exposure to individual agents is provided in Table 5. Treatment history was comparable in the two arms.

Table 5 Prior Treatment

	Panobinostat + BD n=387	Placebo + BD n=381
Median time from initial diagnosis, years (range)	3.1 (0.2, 25.7)	3.2 (0.2, 25.0)
Median # of prior antineoplastic regimens (range)	1 (1, 4)	1 (1, 3)
Prior chemotherapy		
Corticosteroids[1]	347 (89.7%)	341 (89.5%)
Melphalan	310 (80.1%)	301 (79.0%)
Thalidomide	205 (53.0%)	188 (49.3%)
Cyclophosphamide	182 (47.0%)	166 (43.6%)
Bortezomib	169 (43.7%)	161 (42.3%)
Doxorubicin	146 (37.7%)	153 (40.2%)
Lenalidomide	72 (18.6%)	85 (22.3%)
Other prior therapy		
Stem cell transplant	215 (55.6%)	224 (58.8%)
Radiation	93 (24%)	73 (19.2%)

BD = bortezomib + dexamethasone
[1] Includes dexamethasone, prednisolone, betamethasone, corticosteroids, and methylprednisolone
[Source: FDA analysis]

The pathologic features of myeloma in patients on trial are comparable to the current understanding of the disease and are fairly balanced between arms. The percentage of missing serum or urine PEP results is high at baseline which impacts response assessments. Refer to Table 6.

Table 6 Baseline Disease Characteristics

	Panobinostat + BD n=387	Placebo + BD n=381
Immunoglobulin class		
IgG	252 (65.1%)	251 (65.9%)
IgA	90 (23.3%)	86 (22.6%)
IgM	4 (1.0%)	1 (0.3%)
IgD	3 (0.8%)	3 (0.8%)
IgE	0	1 (0.3%)
Involved light chains at initial diagnosis		
Kappa	241 (62.3%)	219 (57.5%)
Lambda	126 (32.6%)	137 (36.0%)
Light chain only disease	24 (6.2%)	19 (5.0%)
Renal impairment[1]	265 (68.5%)	249 (65.4%)
Serum M-protein by PEP	n=300 (77.5%)	n=317 (83.2%)
Median, g/dL (range)	2.2 (0, 8.3)	2.5 (0, 8.4)
Urine M-protein by PEP	n=278 (71.8%)	n=264 (69.3%)
Median, mg/24h (range)	10.5 (0, 21720)	0 (0, 16050)
Bone marrow plasma cell count	n=347 (89.7%)	n=345 (90.6%)
Median, % (range)	20 (0, 100)	25 (0, 99)
Soft tissue plasmacytoma present	21 (5.4%)	19 (5.0%)
Lytic bone lesions present	180 (46.5%)	193 (50.7%)
ECOG Performance Score		
0-1	366 (94.6%)	348 (91.3%)
2	19 (4.9%)	29 (7.6%)

BD = bortezomib + dexamethasone
[1] baseline CrCl 60-90 mL/min. Patients with CrCl <60 mL/min were not eligible.
[Source: FDA analysis]

7.2.2 Patient Disposition

To continue protocol treatment after the first 8 cycles (24 weeks), a response to treatment or stable disease was required, as was no Grade 2 or higher toxicity. Only 44% of patients on the panobinostat + BD arm and 50% of patients on the placebo + BD arm started Treatment phase 2.

A greater percentage of patients (34% vs. 17%) stopped treatment for an adverse event or withdrew consent on the panobinostat + BD arm compared to the placebo + BD arm. Nearly twice the percentage of patients (40%) stopped treatment in the placebo + BD arm for progression of disease compared to the panobinostat + BD arm (21%). Refer to Table 7.

Table 7 Disposition

	Panobinostat + BD n=387	Placebo + BD n=381
Treated	382 (98.7%)	376 (98.7%)
Treatment ongoing	0	0
Started Treatment phase 2	169 (43.7%)	192 (50.4%)
Completed Treatment phases 1 and 2	102 (26.4%)	102 (26.8%)
Discontinued treatment	280 (72.4%)	274 (71.9%)
Adverse event	130 (33.6%)	66 (17.3%)
Progressive disease	82 (21.2%)	153 (40.2%)
Consent withdrawal	34 (8.8%)	18 (4.7%)
Death	21 (5.4%)	17 (4.5%)
Completion of end of study evaluation	346 (89.4%)	364 (95.5%)
Progressive disease	206 (53.2%)	268 (70.3%)
Consent withdrawal	72 (18.6%)	44 (11.5%)
Death	28 (7.2%)	19 (5.0%)
New treatment	27 (7.0%)	19 (5.0%)

BD = bortezomib + dexamethasone
[Source: FDA analysis]

7.2.3 Primary Endpoint

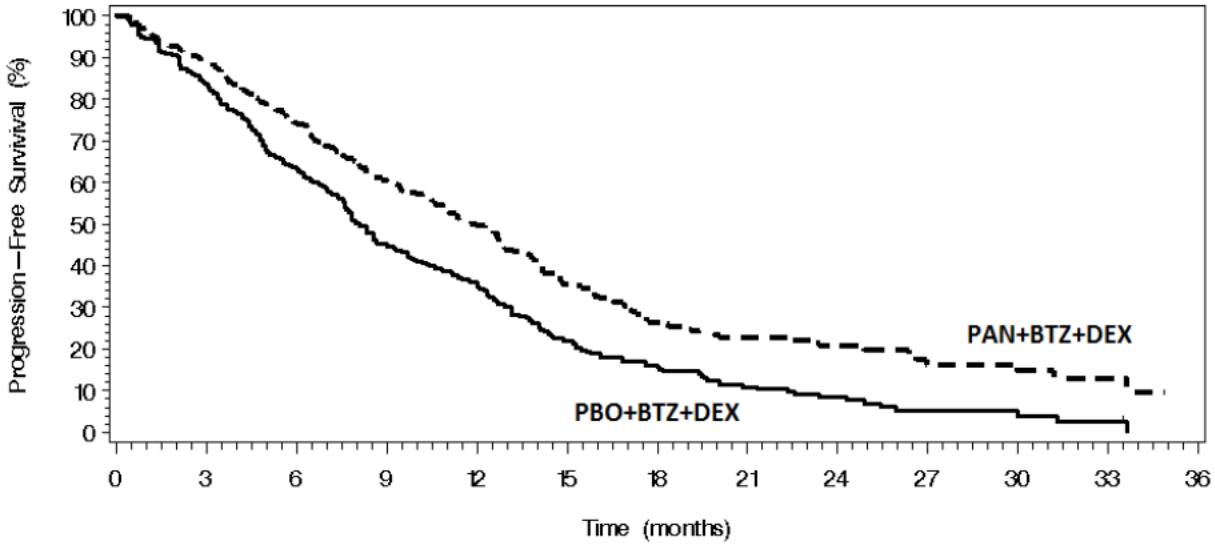
Results of the primary endpoint analysis of PFS are shown in Table 8 and Figure 3. In patients without M-protein measurement by PEP, the investigators could only make a determination of 'progressive disease' or of 'unknown response'. The difference in median PFS as assessed by investigators was 3.9 months favoring the panobinostat + BD arm.

Table 8 Progression-free Survival by Investigator

	Panobinostat + BD n=387	Placebo + BD n=381
PFS events, n	207 (53.5%)	260 (68.2%)
Censored, n	180 (46.5%)	121 (31.8%)
Median time to event, months[1]	12.0 (10.3, 12.9)	8.1 (7.6, 9.2)
Hazard ratio, 95% CI	0.63 (0.52, 0.76)	
p-value	<0.0001	

BD = bortezomib + dexamethasone, CI = confidence interval
[1] Kaplan-Meier estimates
[Source: FDA analysis]

Figure 3 Kaplan-Meier Plot of Progression-free Survival by Investigator



Number of patients at risk

PAN+BTZ+DEX	387	268	202	153	113	76	52	38	26	14	10	5	0
PBO+BTZ+DEX	381	263	185	126	89	51	32	20	12	5	3	1	0

[Source: FDA analysis]

In the PFS analysis, nearly half of patients on the panobinostat + BD arm were censored. Table 9 lists the reasons for PFS censoring by arm. Censoring occurred more often in the panobinostat + BD arm, mostly due to incomplete and missing assessments and to patient withdrawal.

Table 9 PFS Censoring

	Panobinostat + BD n=387	Placebo + BD n=381
Censored patients	180 (46.5%)	121 (31.8%)
Inadequate response assessment	86 (22.2%)	54 (14.2%)
Withdrew consent	74 (19%)	45 (11.8%)
Lost to follow-up	3 (0.1%)	1 (<0.1%)
Other	9 (0.1%)	8 (0.2%)
≥2 missing assessments prior to event	36 (9.3%)	28 (7.3%)
Ongoing (in follow-up)	35 (9.0%)	15 (3.9%)
New cancer therapy added	23 (5.9%)	24 (6.3%)

BD = bortezomib + dexamethasone
[Source: FDA analysis]

The concordance for PFS based on assessment by the investigator versus IRC, was 86% in the panobinostat + BD arm and 83% in the placebo + BD arm. For all confirmed PFS events, 63% in the panobinostat + BD arm were determined to occur at the same time (within 1 week) by both investigators and the IRC, versus 65% in the placebo + BD

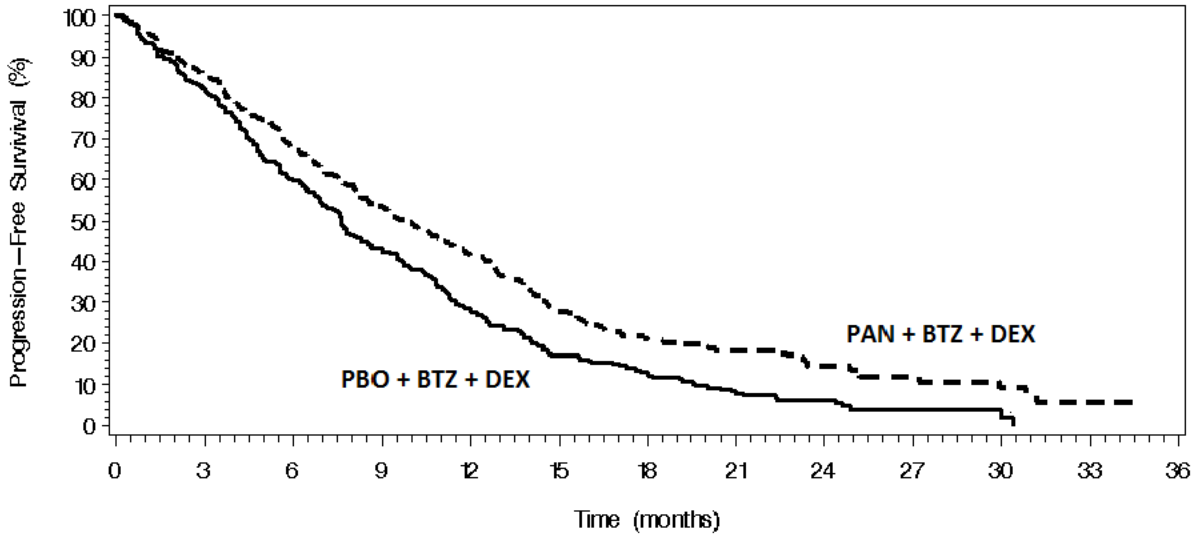
arm. The difference in IRC-assessed median PFS was 2.2 months favoring the panobinostat + BD arm.

Table 10 Progression-free Survival by Independent Review

	Panobinostat + BD n=387	Placebo + BD n=381
PFS events, n	241 (62.3%)	283 (74.3%)
Censored, n	146 (37.7%)	98 (25.7%)
Median time to event, months[1]	9.9 (8.3, 11.3)	7.7 (6.9, 8.5)

BD = bortezomib + dexamethasone
[1] Kaplan-Meier estimates
[Source: FDA analysis]

Figure 4 Kaplan-Meier Plot of PFS by Independent Review



PAN+BTZ+DEX	387	277	194	145	104	65	44	34	20	10	6	2	0
PBO+BTZ+DEX	381	268	182	125	77	44	32	17	9	3	1	0	0

[Source: FDA analysis]

7.2.4 Secondary Endpoints

Overall Survival

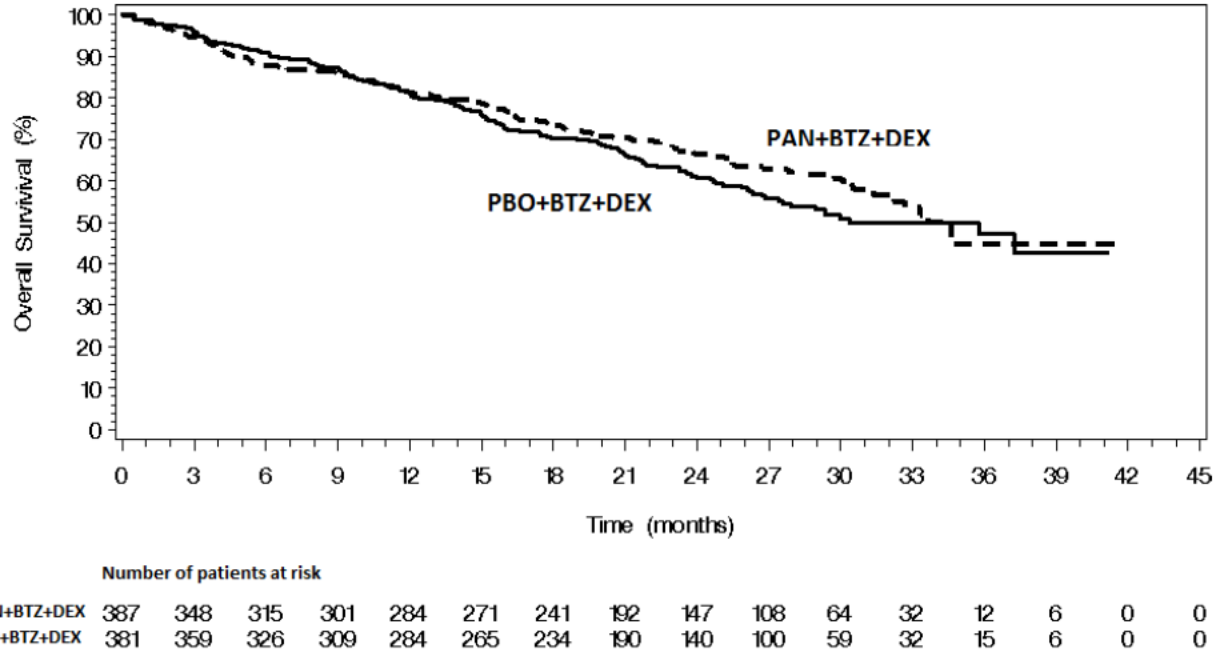
The survival data from the planned interim analysis is not mature. From the data included at the time of the NDA submission, 286 events (69%) were observed. There were fewer deaths reported in the panobinostat + BD arm compared to the placebo + BD arm. At the data cut-off, 416 of the 482 censored patients continued to be followed for survival. The crossing lines in the 3- to 8-month time period suggest that survival favored the placebo + BD arm over the panobinostat + BD arm.

Table 11 Overall Survival

	Panobinostat + BD n=387	Placebo + BD n=381
OS events, n	134 (34.6%)	152 (39.9%)
Censored, n	253 (65.4%)	229 (60.1%)
Median time to event, months[1]	33.6 (31.3, NE)	30.4 (26.9, NE)
Hazard ratio, 95% CI	0.87 (0.69, 1.10)	
p-value	0.2586	

BD = bortezomib + dexamethasone, NE = not evaluable, CI = confidence interval
[1] Kaplan-Meier estimates
[Source: FDA analysis]

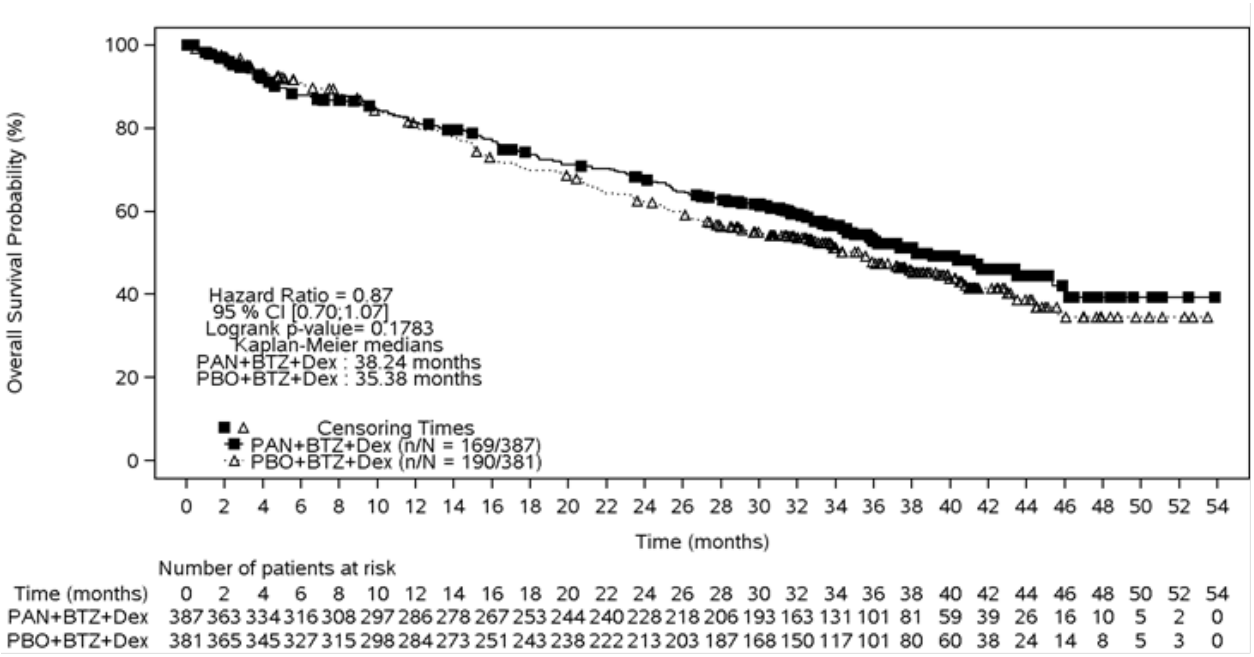
Figure 5 Kaplan-Meier Plot of Overall Survival



[Source: FDA analysis]

From the additional interim analysis amended to the protocol, the Applicant submitted their results to the Agency in September 2014. At the August 2014 data cut-off, 359 events (86.5%) had occurred: 169 in the panobinostat + BD arm and 190 in the placebo + BD arm. Of the 409 censored patients, 342 continued to be followed for survival. The Applicant's plot of OS is included as Figure 6. This data was not analyzed by FDA.

Figure 6 Applicant Kaplan-Meier Plot of Overall Survival



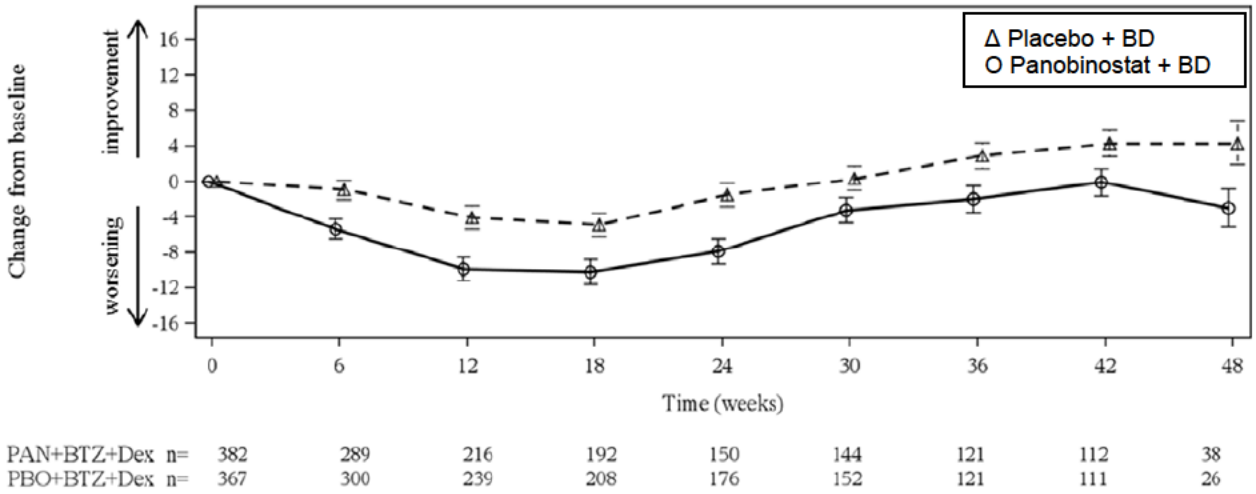
[Source: Novartis CLBH589D2308 submission to FDA on 24 September 2014, p. 6]

Patient-reported Outcomes

In general, missing or incomplete data prohibits a meaningful understanding of patient-reported outcomes. In this trial, among the 3 instruments, baseline data is missing or incomplete for 8-17% of all patients. By the end of study, 27-29% of patients completed the questionnaires with 7-10% disparity between arms. Given the amount of missing or incomplete data in all of the instruments, the PRO results in Trial 2308 should be interpreted with caution.

Global health status/QOL scores for the QLQ-C30 initially declined in both treatment arms, but returned to baseline after week 24 in both arms. Mean changes from baseline exceeded the threshold defined as a minimal important change (> 5 points) in the panobinostat arm. Mean changes in physical functioning, role functioning, social functioning, fatigue, dyspnea, insomnia, appetite loss, and diarrhea were observed in both groups (Figure 7); however, mean changes were generally higher in the panobinostat arm, and may be suggestive of more toxicity.

Figure 7 Mean Changes in QLQ-C30 Patient-reported Symptoms



[Source: Novartis Clinical Study Report CLBH589D2308, p. 198; modified]

Mean change in disease symptoms, as assessed by the myeloma specific module QLQ-MY20, suggested a trend towards improvement, but there was no difference between treatment arms.

In the neurotoxicity subscales of the FACT/GOG-NTX, mean changes from baseline declined in both treatment arms, but was not different between treatment arms. Mean changes improved somewhat over time, but did not fully return to baseline.

7.3 Safety

The safety analysis was performed primarily on the findings from Trial 2308.

An analysis of data pooled from multiple trials of 456 patients exposed to panobinostat, bortezomib, and dexamethasone at the proposed dose for approval was performed. The incidence of specific adverse events did not differ substantially from those identified in Trial 2308.

7.3.1 Patient Characteristics

Table 12 Demographic Characteristics

	Panobinostat + BD n=386	Placebo + BD n=372
Median age, years (range)	63 (28, 84)	63 (32, 83)
Sex		
Male	206 (53.4%)	200 (53.8%)
Female	180 (46.6%)	172 (46.2%)
Race		
White or Caucasian	246 (63.7%)	245 (65.9%)
Asian	129 (33.4%)	101 (27.2%)
Black or African American	5 (1.3%)	17 (4.6%)
Other	6 (1.6%)	9 (2.4%)

BD = bortezomib + dexamethasone
[Source: FDA analysis]

7.3.2 Drug Modifications/Discontinuations

The percentage of patients that discontinued therapy due to an adverse event was higher in the panobinostat arm compared to the placebo arm. Overall 36% (n=139) of patients receiving panobinostat discontinued therapy due to an adverse event compared to 20% of patients (n=76) in the placebo arm. Diarrhea was the most common reason for treatment discontinuation in the panobinostat arm. Adverse events leading to treatment interruption or dose modification occurred in 342 (89%) patients in the panobinostat arm compared to 281 (76%) patients in the control arm. Thrombocytopenia was the most common reason for dose modification or treatment interruption in the panobinostat arm.

7.3.3 Deaths within 30 days of Treatment

On-study deaths (deaths during treatment and within 30 days of the last dose) occurred more frequently in the panobinostat arm compared to the placebo arm, 8% vs. 5.1%. Deaths due to disease progression occurred in 1% of patients in the panobinostat arm, compared to 1.6% in the placebo arm. Death due to causes other than disease progression occurred in 7.0% in the panobinostat arm and 3.5% in the placebo arm. All deaths occurring in the safety population are included in Table 13.

Table 13 Deaths

	Panobinostat + BD n=386		Placebo + BD n=372	
	n	%	n	%
On-Study Deaths	31	8.0	19	5.1
Non Progression	27	7.0	13	3.5
Infection	11	2.8	7	1.9
Hemorrhage	5	1.3	1	0.3
Cardiac Arrest or Failure	4	1.1	3	0.8
Renal	2	0.5	0	0
Sudden Death	1	0.3	0	0
Gastrointestinal	1	0.3	0	0
Neurologic	1	0.3	0	0
Drug Overdose	1	0.3	0	0
Respiratory	1	0.3	2	0.5
Progression	4	1.0	6	1.6

[Source: FDA analysis]

7.3.4 Serious Adverse Events

Nonfatal serious adverse events occurred in 60% of patients in the panobinostat arm and 42% in the placebo arm. SAEs that occurred in ≥2% of patients in the panobinostat arm are summarized in Table 14.

Table 14 Serious Adverse Events

	Panobinostat + BD n=386		Placebo + BD n=372	
	n	%	n	%
Blood and lymphatic system disorders				
Thrombocytopenia	28	7.3	8	2.2
Anemia	15	3.9	3	0.8
Gastrointestinal disorders				
Diarrhea	43	11.1	9	2.4
Vomiting	12	3.1	3	0.8
General disorders and administration site conditions				
Fatigue[1]	26	6.7	6	1.6
Pyrexia	16	4.1	11	3.0
Infections and infestations				
Pneumonia[2]	70	18.1	53	14.2
Sepsis[3]	23	6.0	11	3.0
Urinary tract infection	8	2.1	4	1.1
Metabolism and nutrition disorders				
Dehydration	11	2.8	5	1.3
Hypokalemia	8	2.1	4	1.1
Vascular disorders				
Orthostatic hypotension	9	2.3	1	0.3

[1] Fatigue includes the terms: Fatigue, Malaise, Asthenia, and Lethargy

[2] Pneumonia includes the terms: pneumonia, lower respiratory tract infection, lobar pneumonia, lung infection, pneumonia fungal, pneumonia influenzal, atypical pneumonia, bronchopneumonia, pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia haemophilus, pneumonia pneumococcal, and pneumonia respiratory syncytial viral

[3] Sepsis Includes the terms: sepsis, septic shock, device related sepsis, neutropenic sepsis, streptococcal sepsis, haemophilus sepsis, staphylococcal sepsis, pneumococcal sepsis, candida sepsis

[Source: FDA analysis]

7.3.5 Adverse Events

Adverse events occurred in both arms; however, there was a higher rate of grade 3/4 AEs in the panobinostat arm. Adverse events occurred in 99.7% of patients in both the panobinostat and placebo arms. Grade 3/4 events occurred in 96% of patients in the panobinostat arm compared with 82% in the placebo arm.

Common adverse events that occurred in ≥10% of patients with a ≥ 5% incidence in panobinostat arm compared to the placebo are shown in Table 15. Among these, the most common were diarrhea, thrombocytopenia, anemia, and fatigue.

Grade 3 and 4 adverse events are severe, disabling, or life-threatening. Common grade 3/4 adverse events that occurred in ≥10% of patients with a ≥ 5% incidence in the panobinostat arm compared to the placebo arm include: thrombocytopenia (56.7 vs. 24.7%), diarrhea (25.4 vs. 7.8%), fatigue (24.6 vs. 12.6%), neutropenia (23.8 vs. 8.1%), and hypokalemia (19.2 vs. 6.5%).

Table 15 Adverse Events

	Panobinostat + BD n=386				Placebo + BD n=372			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Blood and lymphatic system disorders								
Thrombocytopenia	249	64.5	219	56.7	151	40.6	92	24.7
Anemia	160	41.5	65	16.8	125	33.6	60	16.1
Neutropenia	114	29.5	92	23.8	40	10.8	30	8.1
Leukopenia	63	16.3	35	9.1	30	8.1	12	3.2
Gastrointestinal disorders								
Diarrhea	264	68.4	98	25.4	153	41.1	29	7.8
Nausea	139	36.0	21	5.4	77	20.7	2	0.5
Vomiting	99	25.6	28	7.3	48	12.9	5	1.3
General disorders and administration site conditions								
Fatigue[1]	230	59.6	95	24.6	158	42.5	47	12.6
Edema peripheral	111	28.8	8	2.1	70	18.8	1	0.3
Pyrexia	100	25.9	5	1.3	55	14.8	7	1.9
Investigations								
Weight decreased	44	11.4	7	1.8	17	4.6	2	0.5
Platelet count decreased	43	11.1	35	9.1	17	4.6	13	3.5

	Panobinostat + BD n=386				Placebo + BD n=372			
	Grade 1-4		Grade 3-4		Grade 1-4		Grade 3-4	
	n	%	n	%	n	%	n	%
Metabolism and nutrition disorders								
Decreased appetite	110	28.5	12	3.1	44	11.8	4	1.1
Hypokalemia	107	27.7	74	19.2	52	14.0	24	6.5
Hyponatremia	49	12.7	37	9.6	19	5.1	13	3.5

[1] Fatigue includes the terms: Fatigue, Malaise, Asthenia, and Lethargy
[Source: FDA analysis]

ECG changes

Treatment-emergent ECG changes occurred in 64% of patients in the Panobinostat arm compared with 42% in the placebo arm. The incidence of QT-prolongation was similar between treatment arms, 12% in the panobinostat arm, and 8% in the placebo arm. New T-wave changes were reported in 40% of patients in the Panobinostat arm compared with 18% in the placebo arm. ST-segment depressions were reported in 22% of patients in the panobinostat arm, compared with 4% in the placebo arm.

8 Summary

This New Drug Application for marketing approval is based primarily on the single randomized efficacy Trial 2308 in patients with relapsed multiple myeloma. Trial 2308 is a randomized, double-blind, placebo controlled trial evaluating the use of panobinostat when added to a backbone of bortezomib and dexamethasone. The primary endpoint is investigator-assessed progression-free survival. PFS was also determined by an IRC in a sensitivity analysis performed to interpret responses for patients with incomplete response assessments. As a consequence, censoring due to missing assessments was reduced in the IRC sensitivity analysis.

The investigator-assessed median PFS difference was 3.9 months. The median PFS was 12 months in the panobinostat + BD arm compared with 8.1 months in the placebo + BD arm, with a hazard ratio of 0.63 (95% CI: 0.52, 0.76; p-value < 0.0001). The IRC-assessed median PFS difference was 2.2 months. The median PFS was 9.9 months in the panobinostat + BD arm compared with 7.7 months in the placebo + BD arm. Overall survival data were not mature.

Deaths within 30 days of treatment occurred more frequently in the panobinostat + BD arm compared to the placebo + BD arm, 8% vs. 5.1%. Deaths within 30 days due to causes other than disease progression occurred in 7% of patients in the panobinostat arm and 3.5% in the placebo arm. Non-fatal serious adverse events occurred in 60% of patients in the panobinostat + BD arm and 42% in the placebo + BD arm. SAEs with a ≥ 5% incidence in the panobinostat + BD arm were: pneumonia, diarrhea, thrombocytopenia, and sepsis.

Advisory Committee advice is requested on the whether the benefit-to-risk ratio is favorable for Farydak given the PFS results and identified safety risks.

9 References

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